December 22, 1995, a statement pursuant to 37 CFR 1.821(f) requesting use of the computer readable form (CRF) submitted in the earlier application, and an amendment to the specification inserting the sequence identifiers. Applicants believe that the application is now in compliance with requirements for nucleotide sequence and/or amino acid sequence disclosures.

Rejection under 35 U.S.C. 112

Claims 45-48 are rejected under 35 U.S.C. 112, first paragraph, as the specification is deemed to not enable one skilled in the art to make and use the claimed invention. The Examiner makes the following arguments in support of his position that the claimed invention is not enabled:

1. The current state of the art does not provide for a vector that routinely achieves a high level of expression of the introduced gene for a prolonged period of time. Thus, the ability to treat diseases using gene therapy has not been established.

2. The physiology of bone formation and resorption is complex and poorly understood. Pathways for bone formation and resorption are not well understood and causes for bone loss are not always known.

3. Because of the lack of knowledge of the underlying factors contributing to bone loss, one cannot predict that osteoprotegerin could reverse a process that causes bone loss. The Examiner argues that the increase in bone density observed in OPG transgenic mice does not relate to gene therapy in patients suffering bone loss.

4. The specification does not provide any working examples of the claimed methods.

5. The claims are broad and encompass any condition resulting in bone loss using any type of vector.

6. Undue experimentation would be required to develop a method for treating bone loss by gene therapy.

Applicants maintain that the present application provides a very strong prediction of the role of osteoprotegerin in the treatment of bone loss, as evidenced by the striking increase in bone density by transgenic mice expressing osteoprotegerin (OPG) (see Example 4 of the specification). This increase in bone density is simply dismissed by the Examiner for no reason whatsoever. The role of OPG in bone loss is further confirmed by the publication of Simonet et al. (Cell 89, 309-319 (1997), attached hereto as Exhibit A) wherein the direct effects of OPG on osteoclasts, specialized cells which resorb bone, are documented. The role of osteoclasts in diseases characterized by bone loss is well established, as evidenced by anti-resorptive compounds which are currently approved drugs for the treatment of osteoporosis and other bone diseases. In addition, the Simonet et al. article provides evidence that administration of OPG protects rats against ovariectomy-induced bone loss (see p. 315 and 316). This evidence strongly suggests that one would predict OPG to be useful for the treatment of bone loss.

It is further observed that undue experimentation would not be required to develop a gene therapy method for treating bone loss with OPG. The Examiner emphasizes the unreliability of expression vectors currently available. Yet, a variety of different types of vectors for gene delivery are available as of the filing date of the application and may be routinely tested with OPG to determine which vectors are appropriate. Previous failures in gene therapy are not prima facie evidence of nonenablement. For example, a number of previous failures have been due to the inability of gene delivery vectors to target appropriate cells, such as targeting tumor cells for the treatment of cancer. Based upon the results disclosed herein, the effects of OPG on bone metabolism are readily apparent simply by increasing

circulating levels of OPG. It is believed that the Examiner has not established a case of nonenablement and the rejection should be withdrawn.

CONCLUSION

In view of the remarks set forth above, Claims 45-48 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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